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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/561,618 | 05/05/2006 | Brenda F. Baker | CORE0005USA | 9771 |

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| EXAMINER | |
|---|---|
| VIVLEMORE, TRACY ANN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |
| **MAIL DATE** | **DELIVERY MODE** |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/561,618 | BAKER, BRENDA F. | |
| | Examiner | Art Unit | |
| | Tracy Vivlemore | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,38,40 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,38,40 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 38 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 11, 79 and 80 of copending Application No. 10/700,689 in view of Brown et al. (US 2003/0166282).

The instant claims are directed to compositions of oligomeric compounds comprising a sense and antisense strand wherein the antisense strand comprises at least one 2'-fluoro nucleoside and the sense strand comprises an inosine base at the 3' terminus and a C or G at the 5' terminus. In specific embodiments the compounds are 12-30 or 19-23 nucleotides in length.

The claims of the '689 application are directed to compositions of sense and antisense strands wherein at least one strand is a chimeric oligomeric compound having at least two 2'-F modified nucleosides. The claims of the '689 application differ from the instant claims in that they do not explicitly recite the presence of one or more inosine nucleobases in the sense strand, including at the 3' terminus. However, the '689 specification contemplates at paragraph 138 the inclusion of modified nucleobases including hypoxanthine, another name for inosine.

Brown et al. teach that the inclusion of nucleotide analogs reduces duplex stability of a siRNA and increases its potency. Brown et al. teach that inosine is one base that will provide this effect and that this nucleoside can be easily incorporated into a nucleic acid using the appropriate phosphoramidite. Therefore, based on the teaching of the '689 application that inosine can be included in a chimeric oligomeric compound and the teachings of Brown that inosine in a siRNA will increase siRNA potency by decreasing duplex stability and the recognition that placement of inosine at a particular position within an oligonucleotide is a matter of design choice, the instant claims are an obvious variation of the claims of the '689 application.

This is a provisional obviousness-type double patenting rejection.

***Claim Rejections - 35 USC § 103***

Claims 1, 38, 40 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. (of record) in view of Brown et al. (US 2003/0166282).

The claims are directed to compositions of oligomeric compounds comprising a sense and antisense strand wherein the antisense strand comprises at least one 2'-fluoro nucleoside and the sense strand comprises an inosine base at the 3' terminus and a C or G at the 5' terminus. In specific embodiments the compounds are 12-30 or 19-23 nucleotides in length or the antisense comprises 2'-fluoro at each nucleotide position.

Fosnaugh et al. teach siRNAs that are about 19 to about 25 nucleotides in length and comprise an antisense region complementary to a sequence encoding a target RNA and a sense region complementary to the antisense region. At paragraph 34 Fosnaugh et al. teach the use of chemically modified siRNAs, with chemical modifications including 2'-deoxy-2'-fluoro ribonucleotides, which improve the stability of the interaction with the target RNA sequence and to improve nuclease resistance. Fosnaugh et al. additionally teach that "universal bases" may be included in a siRNA, teaching at paragraph 129 that inosine is an example of a universal base. At paragraph 50 Fosnaugh et al. teach that 2'-deoxy-2'-fluoro modified nucleotides and universal base modifications can be present in either the sense strand, the antisense strand or both strands and in Table III specifically teach 21 nucleotide siRNAs wherein the antisense strand comprises 2'-fluoro nucleosides and a G at the 5' terminus. Fosnaugh et al. teach modifications to nucleotides in a permissive manner, describing at paragraph 43 for example that a siRNA can comprise any naturally or non-naturally occurring nucleobase and also describing at paragraph 50 that a siRNA can comprise "5 or more" 2'-fluoro nucleotides, but Fosnaugh et al. does not explicitly teach a siRNA wherein every position contains a 2'-fluoro modified nucleotide, nor does this reference explicitly teach the inclusion of inosine at the 3' terminus of the sense strand.

Brown et al. teach siRNAs comprising modified nucleotides that have the effect of decreasing the duplex stability of the dsRNA. Brown et al. teach at paragraph 29 that such siRNAs are significantly more potent. At paragraph 33 Brown et al. teach that because I:C base pairs form only two hydrogen bonds instead of the three in G:C base-

pairs, substitution of inosine (I) for G at one or more positions in the siRNA will reduce duplex stability and thereby enhance siRNA potency. At paragraph 196 Brown et al. teach that inosine can be substituted for guanosine in any siRNA sequence by using an appropriate inosine phosphoramidite.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs comprising 2'-fluoro modified nucleosides as taught by Fosnaugh et al. with one or more inosine bases that will reduce duplex stability as taught by Brown et al. Brown et al. provide a motivation to include inosine nucleotides in a siRNA by teaching that use of such an analog will reduce duplex stability and increase potency of the siRNA and provides a reasonable expectation of success in making siRNAs comprising inosine by teaching that inosine can be easily substituted for guanosine using an appropriate phosphoramidite. Based on the permissive manner in which Fosnaugh et al. teach the inclusion of 2'-fluoro modified nucleotides and the knowledge that such nucleotides can be incorporated into an oligomer using commercially available reagents and routine synthetic methods, one of ordinary skill in the art would recognize the production of a siRNA comprising 2'-fluoro nucleotides at every position of the antisense strand to be a matter of design choice that would be made in the course of routine optimization. Based on the suggestión by Brown et al. of including inosine nucleotides in a siRNA and their teaching that such nucleosides are easily substituted for guanosine using routine synthetic methods and readily available reagents, one of ordinary skill in the art would recognize that placement of the inosine at any particular position, including the 3' terminus of the sense

strand, is a matter of design choice that would be made in the course of routine optimization.

Thus, the invention of claims 1, 38, 40 and 58 would have been obvious, as a whole, at the time the invention was made.

Claims 1, 38, 40 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. (of record) in view of Zamore et al. (US 2005/0181382).

The claims are directed to compositions of oligomeric compounds comprising a sense and antisense strand wherein the antisense strand comprises at least one 2'-fluoro nucleoside and the sense strand comprises an inosine base at the 3' terminus and a C or G at the 5' terminus. In specific embodiments the compounds are 12-30 or 19-23 nucleotides in length or the antisense comprises 2'-fluoro at each nucleotide position.

Fosnaugh et al. teach siRNAs that are about 19 to about 25 nucleotides in length and comprise an antisense region complementary to a sequence encoding a target RNA and a sense region complementary to the antisense region. At paragraph 34 Fosnaugh et al. teach the use of chemically modified siRNAs, with chemical modifications including 2'-deoxy-2'-fluoro ribonucleotides, which improve the stability of the interaction with the target RNA sequence and to improve nuclease resistance. Fosnaugh et al. additionally teach that "universal bases" may be included in a siRNA, teaching at paragraph 129 that inosine is an example of a universal base. At paragraph

50 Fosnaugh et al. teach that 2'-deoxy-2'-fluoro modified nucleotides and universal base modifications can be present in either the sense strand, the antisense strand or both strands and in Table III specifically teach 21 nucleotide siRNAs wherein the antisense strand comprises 2'-fluoro nucleosides and a G at the 5' terminus. Fosnaugh et al. teach modifications to nucleotides in a permissive manner, describing at paragraph 43 for example that a siRNA can comprise any naturally or non-naturally occurring nucleobase and also describing at paragraph 50 that a siRNA can comprise "5 or more" 2'-fluoro nucleotides, but Fosnaugh et al. does not explicitly teach a siRNA wherein every position contains a 2'-fluoro modified nucleotide, nor does this reference explicitly teach the inclusion of inosine at the 3' terminus of the sense strand.

Zamore et al. teach asymmetric siRNAs that provide enhanced specificity and efficacy for mediating RISC-mediated cleavage of a desired target gene. These siRNAs are described at paragraphs 80-82. In one preferred aspect the base pair strength between the antisense strand 5' end and the sense strand 3' end of the siRNAs is less than the bond strength or base pair strength between the antisense strand 3' end and the sense strand 5' end, such that the antisense strand preferentially guides cleavage of a target mRNA. In one embodiment, the bond strength or base pair strength is less due to at least one base pair comprising a rare nucleotide such as inosine (I). These teachings are present in the provisional application filed June 2, 2003.

Zamore et al. demonstrate this concept in example IV, producing siRNAs having I:C base pairs at the 5' terminus of the antisense strand. When the 5' terminus of the anti-sense strand is substituted with inosine the anti-sense strand was enhanced

relative to the sense strand. Thus, the strand whose 5' end is in the weaker base pair was more effective at target cleavage.

At paragraphs 89-92 Zamore et al. further teach that the siRNAs can be modified to improve stability in serum or in growth medium for cell cultures. Preferred nucleotide analogues include sugar-modified ribonucleotides where the 2'OH-group is replaced by groups such as halo, which includes fluorine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs comprising 2'-fluoro modified nucleosides as taught by Fosnaugh et al. with an inosine base that will produce asymmetry within the siRNA as taught by Zamore et al. Both Fosnaugh et al. and Zamore et al. suggest the use of 2'-modified nucleosides such as fluoro for the purposes of increasing nuclease resistance and Fosnaugh actually produces siRNAs where these modifications are in the antisense strand. Based on the permissive manner in which Fosnaugh et al. teach the inclusion of 2'-fluoro modified nucleotides and the knowledge that such nucleotides can be incorporated into an oligomer using commercially available reagents and routine synthetic methods, one of ordinary skill in the art would recognize the production of a siRNA comprising 2'-fluoro nucleotides at every position of the antisense strand to be a matter of design choice that would be made in the course of routine optimization. Zamore et al. provide a motivation and reasonable expectation of success in including inosine nucleotides in a siRNA by teaching and exemplifying that inclusion of such a nucleoside reduces the base pairing strength and provides a motivation to reduce the base pair strength between the antisense 5' end and the sense 3' end by teaching that

reducing strength of this particular base pair enhances cleavage of the target mRNA. While Zamore et al. exemplify the use of inosine in the antisense strand and not the sense strand, one of ordinary skill in the art would recognize that reversing the I:C base pair to place the inosine in the sense strand produces an equivalent structure that is also an asymmetric siRNA having an enhanced antisense strand.

Thus, the invention of claims 1, 38, 40 and 58 would have been obvious, as a whole, at the time the invention was made.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
December 12, 2007